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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,787	01/21/2004	David M. Weiner	ACADIA.031A	3544

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
05/20/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/761,787	WEINER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 59-101* is/are pending in the application.

4a) Of the above claim(s) *59, 61-64, 93, 94, 100 and 101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 60,65-92 and 95-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/14/07;12/20/07;3/3/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed January 22, 2008 have been received and entered into the application.

Applicants' arguments have been considered but are moot in view of the new ground(s) of rejection.

It is noted that claims 1-9, 60 and 65-92, 95-99 have been examined to the extent of Applicants' elected invention of the treatment of psychosis with elected species, Aripiprazole, as an additional therapeutic agent. Newly added claims 93-94, 100 and 101 are withdrawn from consideration.

Newly submitted claims 93-94, 100 and 101 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

(one or more of the following reasons apply):

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 93-94, 100 and 101 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. The above statement refers to Applicants' amendment made of record on October 18, 2007. It is noted that the Examiner sent an action dated October 14, 2007 in response to Applicants' previous amendment made of record on August 6, 2007.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 82-92, 95-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treating, controlling, ameliorating psychosis", does not reasonably provide enablement for the "reducing the **risk** of psychosis". The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

2. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating, controlling, ameliorating or reducing the risk of psychosis in a patient in need thereof that comprises adminsitering to the patient a therapeutically effective amount of a muscarinic M1 receptor ectopic activator. The nature of the invention is extremely complex in that it encompasses the actual reduction of the risk of psychosis (i.e. schizophrenia) such that the subject treated with above compounds does not contract psychosis.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass reducing risk of psychosis in humans which has potentially many different causes (i.e. many different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually reduce the risk of psychosis is minimal. All of the guidance provided by the specification is directed towards treatment rather than reducing the risk of psychosis.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than reducing the risk of psychosis.

State of the Art: While the state of the art is relatively high with regard to treatment of psychotic disorder (i.e. schizophrenia), the state of the art with regard to reducing the risk of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to reduce the risk of development of psychosis. The state of the art, Rozen (U.S.Patent No. 6,566,065 B1) teaches that although genetic factors are known to play a role in the etiology of the most common psychosis, i.e. schizophrenia, identification of susceptibility genes has been difficult because of variability of the schizophrenia phenotype, including variations in severity of symptoms, response to medications, and long term outcome. (column 35, lines 60-65). Therefore, instant claims drawn to reducing the risk of such disorder is highly speculative.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual reduction of the risk of having psychosis in a

human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of reducing the risk of psychosis.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for reducing the risk of psychosis. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard reducing the risk of psychosis with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding reducing the risk of psychosis with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to reducing the risk of psychosis in a subject by administration of one of the claimed compounds.

Therefore, a method of treating, controlling, ameliorating or reducing the risk of psychosis in a patient in need thereof that comprises adminsitering to the patient a

therapeutically effective amount of a muscarinic M1 receptor ectopic activator is not considered to be enabled by the instant specification.

Written Description

Claims 82-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 82-91 are drawn to a method of treating, controlling, ameliorating or reducing the risk of psychosis in a patient in need thereof that comprises administering to the patient a therapeutically effective amount of **a muscarinic M1 receptor ectopic activator**. The claims thus encompass a broad genus of **a muscarinic M1 receptor ectopic activator** which must have the property of also being antipsychotic inducing compound.

The instant specification does not describe or exemplify any **muscarinic M1 receptor ectopic activator**, much less any **muscarinic M1 receptor ectopic activator** which functions to reduce psychosis. This instant specification therefore does not provide a basis for one of skill in the art to **envision the structural/functional characteristics of such a compound**. The prior art does not provide basis for one of skill in the art to envision **a muscarinic M1 receptor ectopic activator** that would necessary comprise antipsychotic characteristics. **A muscarinic M1 receptor ectopic activator** is in a number different signal transduction pathways in the cell having

different effects on a cell physiology. Therefore there is no basis to predict any analgesic effects of a particular activator affecting particular pathway.

Given the broad of genus of **a muscarinic M1 receptor ectopic activator** encompassed by the rejected claim, and given the lack of a basis provided by instant specification or prior art to envision **a muscarinic M1 receptor ectopic activator** that are necessary capable of inducing antipsychotic activity, one of skill in the art would not have been able to envision a sufficient number of **a muscarinic M1 receptor ectopic activator** possessing antipsychotic characteristics to describe broadly claimed genus. Therefore, one of skill in the art would reasonably have concluded Applicants' were not in possession of the claimed invention **(a muscarinic M1 receptor ectopic activator)**.

New Matter

Claims 82-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "reducing the risk of psychosis" (see claims 82), the phrase "a muscarinic M1 receptor ectopic activator" (see claims 82, 85, 86-92), the phrase "**selective** muscarinic M1 receptor ectoic activator"(see claims 86 and 99), the phrase "**acts at a different site than the orthosteric site** of the muscarinic M1 receptor" (see claim 88), the phrase "possesses an EC50 for binding to the muscarinic M1 receptor of

1uM or less as evaluated by the muscarinic FLIPR assay" (see claim 89), the term "orally" (claim 90), and the phrase "a non-peptidal muscarinic M1 receptor ectopic activator" (see claim 91) lack literal support in the specification as originally filed.

This is a New Matter rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-9, 60, 65-92, 95-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmutz et al. (U.S.Patent No. 3,758,479) of record in view of Tamminga et al. (2002).

Schmutz et al. teach that N-desmethylclozapine is useful as a neuroleptic agent. (column 1, lines 29-40, column 17, Example 71). Schmutz et al. teach that N-desmethylclozapine can be administered in the form of pharmaceutical preparations including tablets or solutions for injection. (column 10, lines 1-7).

Schmutz et al. do not expressly teach the treatment of psychosis including specific symptoms of psychosis, the mechanism of action of increasing a level of activity of a muscarinic receptor, effective amounts, combination with Aripiprazole, and the subject having additional medical condition set forth in claims 74-75.

Tamminga et al. teach that Aripiprazole is useful for the treatment of psychosis because it delivers full antipsychotic action equal to haloperidol. (abstract, page 144

under C. Aripiprazole). Tamminga et al. teach that psychosis is a symptom of abnormal mental function characterized by thought disorder, paranoia, hallucinations delusions and dementia. Tamminga et al. teach that Aripiprazole has advantages in the treatment of affect control and cognitive performance. (abstract, last sentence).

It would have been obvious to one of ordinary skill in the art to employ N-desmethylclozapine for the treatment of symptoms of psychosis because Schmutz et al. teach that N-desmethylclozapine is suitable for the treatment of psychotic conditions. One would have been motivated to employ N-desmethylclozapine for the treatment of symptoms of psychosis taught by Tamminga et al. in order to achieve an expected benefit of effectiveness of N-desmethylclozapine in the treatment of psychotic conditions taught by Schmutz et al. Moreover, to further combine Aripiprazole in the treatment of psychosis with N-desmethylclozapine would have been obvious because Aripiprazole is also useful for the treatment of psychosis and advantages in cognitive performance in view of Tamminga et al. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Further, the mechanism of action of increasing a level of activity of muscarinic receptor set forth in claim 1 is obvious because a mechanism by which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method. The patient, condition (psychosis) to be treated and the effect are the same. With regard to the psychosis patient being treated having neurodegenerative conditions such as Alzheimer does not make unobvious because a

patient suffering from such disorder generally suffers and has symptoms of psychosis and cognitive dysfunction.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9, 60 and 65-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-21 of copending Application No. 10/913,117; claims 1-6 and 19-29 of copending Application No. 11/098,892; claims 1-8 of copending Application No. 11/671,405; and claims 1-5 and 15 of copending Application No. 11/416,565. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass

the same subject matter of treating psychotic condition or symptoms of psychosis comprising the same active agent N-desmethylclozapine. As such, the claims of the instant Application and the claims in the copending Applications would have been obvious variations of the other to one of ordinary skill in the art. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

None of the claims are allowed.

Applicants' submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 20, 2007 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
April 22, 2008